



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Margret Oethinger *et al.*

Serial No.: 10/629,340

Filed: July 28, 2003

For: METHODS OF REDUCING MICROBIAL  
RESISTANCE TO DRUGS

Attorney Docket No.: PKZ-035CPA2CN2

Group Art Unit: 1654

Examiner: Louise N. Leary

MS Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

**INFORMATION DISCLOSURE STATEMENT**


Dear Sir:

For the Examiner's convenience in reviewing this continuation application, Applicants submit a consolidated PTO Form 1449, listing all references cited during the prosecution of the parent application. The present application is a Continuation of U.S. Serial No. 09/966,835, filed September 28, 2001 (Atty. Docket No. PKZ-035CPA2CN). All references listed on the enclosed PTO Form 1449 have been previously cited by or submitted to the Office in the prior application, and, in accordance with 37 CFR §1.98(d), copies of the references are not enclosed but will be provided upon request.

This statement is not to be interpreted as a representation that the cited publications are material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any publication herein be construed *per se* as a representation that such publication is prior art. Moreover, Applicants understand that the Examiner will make an independent evaluation of the cited publications.

In accordance with 37 CFR §1.97(c)(2) and §1.17(p), please charge the \$180.00 submission fee to our Deposit Order Account No. 12-0080. Please charge any necessary additional fees or credit any overpayments to our Deposit Order Account No. 12-0080.

Respectfully submitted,  
LAHIVE & COCKFIELD, LLP

  
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Date: December 1, 2004

EAH/MEW/CRC/gpc  
Enclosures

APPLICANT FACSIMILE OF FORM PTO-1449  
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EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	A1	4,806,529	2/89	Levy	514	154	
	A2	5,021,407	6/91	Levy	514	154	
	A3	5,064,821	11/91	Levy	514	154	
	A4	5,179,096	01/93	Gentilini et al.	514	253	
	A5	5,258,372	11/93	Levy	514	154	
	A6	5,589,470	12/96	Levy	514	154	
	A7	5,789,188	8/98	Rothstein, et. al.	435	29	
	A8	5,811,412	9/98	Levy	514	154	
	A9	5,817,793	10/98	Levy	536	24.1	
	A10	5,989,832	11/99	Trias et al.	435	7.2	
	A11	6,068,972	5/00	Levy	435	4	

## FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
	A12	WO 96/33285	10/96	PCT				
	A13	WO 99/37667	01/99	PCT				
	A14	WO 99/17607	04/99	PCT				
	A15	WO 99/17760	04/99	PCT				
	A16	WO 99/17791	04/99	PCT				
	A17	WO 99/32657	07/99	PCT				
	A18	WO 99/37800	07/99	PCT				
	A19	WO 00/01714	01/00	PCT				
	A20	WO 00/32196	06/00	PCT				
	A21	WO 96/23075	08/00	PCT				

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	A22	Aono, Rikizo (1998) "Improvement of Organic Solvent Tolerance Level of Escherichia Coli by Overexpression of Stress-Responsive Genes", Extremophiles Vol. 2 p. 239-248;
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<p>*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.</p>		

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		Brenwald, N.P. et al. Fluoroquinolone Resistance in Streptococcus pneumoniae by an Efflux Mechanism, Abstr of the 37 <sup>th</sup> Inersc. Conference on Antimicrobial Agents and Chemotherapy;
	B2	Buyse, J.M. et al. (1996) "Mutation of the AcrAB antibiotic efflux pump in Escherichia coli confers susceptibility to oxazolidinone antibiotics" Abstracts of the Interscience Conference Of Antimicrobial Agents And Chemotherapy, Vol. 36, No. 0, pp. 41. 36 <sup>th</sup> ICAAC (International Conference of Antimicrobial Agents and Chemotherapy) New Orleans, Louisiana, USA. September 15-18;
	B3	Cohen, Seth P. et al. (1989) "Cross-Resistance to Fluoroquinolones In Multiple-Antibiotic-Resistant (Mar) Escherichia Coli Selected By Tetracycline Or Chloramphenicol: Decreased Drug Accumulation Associated With Membrane Changes In Addition To OmpF Reduction" Antimicrobial Agents and Chemotherapy, Vol. 33, No. 8, pp. 1318-1325;
	B4	Fournier, B. et al. A mutation in the griB Gene of topoisomerase IV from Staphylococcus aureus Causes an Increase of Fluoroquinolone Resistance and A Decrease of coumarin Resistance, Abstracts of the 37 <sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy;
	B5	Goldman, John D. (1996) "Multiple Antibiotic Resistance (mar) Locus Protects Escherichia Coli From Rapid Cell Killing by Fluoroquinolones" Antimicrobial Agents and Chemotherapy, Vol. 40, No. 5, pp. 1266-1269;
	B6	Gustafson, John E. et al. (1999) "Growth In The Presence of Salicylate Increases Fluoroquinolone Resistance In Staphylococcus Aureus" Antimicrobial Agents and Chemotherapy, vol. 45, No. 4 pp. 990-992;
	B7	Hooper DC, et al. (1987) "Mechanisms of action of and resistance to ciprofloxacin". Am J Med 82(4A);
	B8	Hullen, V. et al. (1998) "Induction of the mar Phenotype Is a Possible Cause for The Development of Fluoroquinolone Resistance In Escherichia Coli," Antimicrob. Resist. Action;
	B9	Kern, W.V. et al. Selection of high-level fluoroquinolone-resistant Escherichia coli mutants in-vitro: involvement of the mar or Sox system, Abstracts of the 37 <sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy;
	B10	Levy, Colin W et al. (1999) "Molecular Basis of Triclosan Activity" Nature, Vol. 398, pp. 383-384;
	B11	Lewis, Kim et al. (1996) "Multidrug Resistance Pumps Provide Broad Defense" ASM News, Vol. 63, No. 11 pp. 605-610;
	B12	Lewis, Kim (1994) "Multidrug Resistance Pumps In Bacteria; Variations On a Theme" TIBS 19, pp. 119-123;
	B13	Lomovskaya, O. et al. "Identification and characterization of Efflux Pump Inhibitors in P. aeruginosa", Abstract no. F-1264, Poster Presentation at the 38 <sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy;
	B14	Lomovskaya, O. et al. "Inhibitors of Efflux Pumps in Pseudomonas aeruginosa Potentiate the Activity of the Fluoroquinolone Antibacterial Levofloxacin", Abstract no. F-1265, Poster Presentation at the 38 <sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy;
	B15	Lomovskaya, O. et al. "Efflux Pump Inhibitors (EPIs) Enhance the Activity of antimicrobial Agents against a random Selection of Bacteria", Abstract no. F-1266, Poster Presentation at the 38 <sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy

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APPLICANT FACSIMILE OF FORM PTO-1449  
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C1	Lomovskaya, O. et al. "Prevalence of Efflux Pump Overexpression Among Clinical Isolates of Pseudomonas Efflux Pump Inhibitors (EPIs) Enhance the Activity of antimicrobial Agents against a random Selection of Bacteria", Abstract no. F-1267, Poster Presentation at the 38 <sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy
C2	Lomovskaya, O. et al. "Potentiation of Levofloxacin (levo) by a Broad-Spectrum Efflux Pump Inhibitor (EPI) in Mouse Models of Infection Due to Pseudomonas aeruginosa", Abstract no. F-1268, Poster Presentation at the 38 <sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy;
C3	Lomovskaya, O. et al. "Inhibitors of Fungal Efflux Pump", Abstract no. F-1269, Poster Presentation at the 38 <sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy
C4	Lomovskaya, Olga et al. (1999) "Use of a Genetic Approach To Evaluate the Consequences of Inhibition of Efflux Pumps in Pseudomonas Aeruginosa" Antimicrobial Agents and Chemotherapy, Vol. 43, No. 6, pp. 1340-1346;
C5	Markham PN, et al. (1999) "Multiple novel inhibitors of the NorA multidrug transporter of Staphylococcus aureus. <i>Antimicrob Agents Chemother.</i> ;43(10):2404-8.
C6	Ma, Dzwokai et al. (1995) "Genes acrA and acrB Encode A Stress-Induced Efflux System of Escherichia Coli" Molecular Microbiology Vol. 16, No. 1, pp. 45-55;
C7	Ma, Dzwoka et al. (1996) "The Local Repressor AcrR Plays A Modulating Role In The Regulation of acrAB Genes of Escherichia Coli by Global Stress Signals" Molecular Microbiology, Vol. 19, No. 1, pp. 101-112;
C8	McMurry, Laura et al. (1998) "Overexpression of marA, soxS, or acrAB produces resistance to triclosan in Escherichia coli: FEMS Microbiol. Lett. 166(2), 305-309;
C9	McMurry, Laura et al. (1994) "Active Efflux of Chloramphenicol In Susceptible Escherichia Coli Strains and in Multiple-Antibiotic-Resistant (Mar) Mutants" Antimicrobial Agents and Chemotherapy, Vol. 38, No. 3, pp. 542-546;
C10	Miller, Paul F and Sulavik, Mark C. (1996) "Overlaps and Parallels In The Regulation of Intrinsic Multiple-Antibiotic Resistance In Escherichia Coli" Molecular Microbiology, Vol. 21, No. 3, pp. 441-448;
C11	Moken, Merri C. et al. (1997) "Selectin of Multiple-Antibiotic-Resistant (Mar) Mutants of Escherichia Coli by Using the Disinfectant Pine Oil: Roles of the mar and acrAB Loci" Antimicrobial Agents and Chemotherapy Vol. 41, No. 12, pp. 2770-2772;
C12	Nikaido, Hiroshi (1996) "Multidrug Efflux Pumps of Gram-Negative Bacteria" Journal of Bacteriology Vol. 178, No. 20 pp. 5853-5859;
C13	Nikaido, Hiroshi et al. (1998) "Multidrug Efflux Pump AcrAB of Salmonella Typhimurium Excretes Only Those $\beta$ -Lactam Antibiotics Containing Lipophilic Side Chains" Journal of Bacteriology, Vol. 180, No. 17, pp. 4686-4692;
C14	Oethinger, M. et al., (1998) "Ineffectiveness of Topoisomerase Mutations in <i>Escherichia coli</i> in the Absence of the AcrAB Multidrug Efflux Pump" Presented at the 38 <sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy; September 24-27, 1998 in San Diego, CA. (Abstract no. C125);

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D1	Oethinger, Margret et al. (1998) "Overexpression of the marA or soxS Regulatory Gene in Clinical Topoisomerase Mutants of Escherichia Coli" Antimicrobial Agents and Chemotherapy, Vol. 42, No. 8 pp. 2089-2094;
D2	Oethinger, Margret et al. (1998) "Associate of Organic Solvent Tolerance and Fluoroquinolone Resistance In Clinical Isolates of Escherichia Coli" Journal of Antimicrobial Chemotherapy, Vol. 41, pp. 111-114;
D3	Okusu, Haruko et al. (1996) "AcrAB Efflux Pump Plays a Major Role in the Antibiotic Resistance Phenotype of Escherichia Coli Multiple-Antibiotic-Resistance (Mar) Mutants" Journal of Bacteriology Vol. 178, No. 1 pp. 306-308;
D4	Park, Yoon-Hee et al. (1996) "Molecular Analysis of Fluoroquinolone-Resistance in Escherichia Coli on the Aspect of Gyrase and Multiple Antibiotic Resistance (mar) Genes" Medical Journal, Vol. 39, No. 4 pp. 514-540;
D5	Paulsen, Ian T. et al. (1996) "Proton-Dependent Multidrug Efflux Systems" Microbiological Reviews Vol. 60, No. 4 pp. 575-608;
D6	Sanchez, Laura et al. (1997) "The <i>acrAB</i> Homolog of Haemophilus influenzae Codes for a Functional Multidrug Efflux Pump, Vol 179(21), pp. 6855-6857;
D7	Schmitz, Franz-Josef et al. (1998) "The Effect of Reserpine, An Inhibitor of Multidrug Efflux Pumps, On The In-Vitro Activites of Ciprofloxacin, Sparfloxacin and Moxifloxacin Against Clinical Isolates of Staphylococcus Aureus" Journal of Antimicrobial Chemotherapy Vol. 42, pp. 807-810;
D8	Spratt, Brian G. (1994) "Resistance to Antibiotics Mediated by Target Alterations" Science Vol. 264, pp. 388-392;
D9	Sun, Li et al. (1996) "NorA Plasmid Resistance to Fluoroquinolones: Roles of Copy Number and norA Frameshift Mutations" Antimicrobial Agents and Chemotherapy Vol. 40, No. 7, pp 1665-1669;
D10	Tanaka, Toshihiko et al. (1997) "RobA-induced multiple antibiotic resistance largely depends on the activation of the AcrAB efflux" Microbiol. Immunol. 41(9), 697-702;
D11	Tankovic J, et al. (1996) "Contribution of mutations in gyrA and parC genes to fluoroquinolone resistance of mutants of Streptococcus pneumoniae obtained in vivo and in vitro" Antimicrob Agents Chemother;40(11):2505-10;
D12	White, David G. et al. (1997) "Role of the <i>acrAB</i> Locus In Organic Solvent Tolerance Mediated By Expression of <i>marA</i> , <i>soxS</i> , or <i>robA</i> in Escherichia Coli" Journal of Bacteriology Vol. 179, No. 19 pp 6122-6126.

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	E1	6,326,391	12/01	Markham <i>et al.</i>	514	410	
	E2	6,346,391	02/02	Oethinger <i>et al.</i>	435	32	

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